# Prediction research of outcome in neuroleptic treatment – definitions and concepts

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## Introduction

Prognosis is a core concept in medicine. It is a prerequisite for the clinical evaluation of spontaneous course and effective treatment. Since the introduction of effective treatment methods in psychiatry, interest in prediction of outcome as well as understanding the factors contributing to variability of response to therapy has preoccupied researchers and clinicians. One reason for the limitation of results thus far is the inconsistent conceptual and methodological foundation of research.

Successful research on response prediction requires explicit concepts, definitions and operationalizations of illness course (spontaneous "prognosis"), response, dimensions of outcome, and predictors. In addition appropriate statistical methods are also required for analysing their relationship. A superordinate concept of prediction has to make explicit how these elements relate to each other in bio-psycho-social terms. Finally, valid predictions can only be made if there are recognizable rules operative in illness course and treatment outcome. Hence, the more we learn about the pathophysiology of the illness, its course and potential determinants the better we will be able to develop a valid predictive algorithm.

In this contribution the following conceptual and methodological aspects of prediction research will be discussed:

- Treatment outcome and response
- Predictors
- Predictor-outcome relationship

## Treatment outcome

The outcome of schizophrenia is the result of an as yet poorly under-

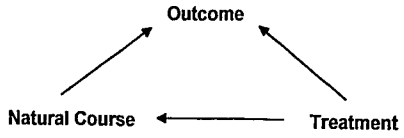



**Fig. 1.** Interaction of natural course and treatment in the development of illness outcome

stood interaction of biological and non-biological processes building up the "natural course", which is further "complicated" by treatment influences (Fig. 1).

Methodological factors contribute heavily to the characteristics of "outcome" and related measures such as treatment response. Measurement of outcome therefore requires a multidimensional conceptual framework, appropriate instruments, and adequate timing of assessment.

### *Illness course*

To model the true continuum of the illness course with respect to time coordinates ($t_1$, $t_2 \ldots t_n$) a sufficiently close time frame of assessment ($\delta t \rightarrow 0$) is required (see Fig. 3). Depending on the illness stage (acute/postacute/chronic) and the corresponding gradient of change to be expected a relatively narrow time frame should be chosen. However, since assessment instruments usually cover a certain time period in retrospect, a too narrow time frame is neither necessary nor feasible to model the illness course longitudinally with respect to certain treatment conditions.

### *Outcome*

"Outcome" refers to a cross-sectional aspect of the illness course either under spontaneous conditions or after a certain treatment intervention. According to a multidimensional concept of outcome, measures are required for different target areas sensitive to the applied treatment. Again, depending on the stage of illness/treatment (e. g. acute vs long-term) varying target areas have to be assessed. Main areas to be covered are symptomatology, work function, social contacts, need for and duration of hospitalization. Quality of life – although inconsistently defined – is another outcome concept related to social adaptation, subjective well-being and treatment side effects and which has recently been given more attention in drug studies (Awad 1992). Both self-ratings as well as observer-ratings can be employed. In schizophrenia various outcomes are cross-sectionally moderately intercorrelated but are best predicted longitudinally by themselves (Gaebel et al. 1986). Therefore, having been conceptualized as "open linked systems", according to Strauss and

Carpenter (1974) "each system is open in the sense of influencing and being influenced by outside variables; the systems are linked in the sense of having definite but incomplete interdependence; conceived in this framework each outcome process, work, social relationships, symptoms, and need for hospitalization might be considered as a system". Accordingly, at a given point in time there are many outcomes instead of a single outcome.

The characterization of a biological variable as a state- or trait-marker depends not the least on a clear definition of the pre-, intra- and post-episodic illness state by means of a target symptom measure. Schizophrenic patients remitted on a positive symptom scale often still demonstrate substantial negative symptoms. It therefore depends on our definition, whether we call these patients remitted or not and hence declare a variable as a state- or trait-marker.

Hence there is no outcome besides what is arbitrarily defined as such and is applied at a certain time point of the illness course.

### *Response*

Response is clearly a treatment-related concept of illness course. It refers to an either pre- or post-treatment defined change of illness course in a certain outcome system due to the influence of treatment. However, a causal treatment influence may only be inferred, if an appropriate study design (e. g. a randomly assigned placebo group) allows to control for spontaneous change in the illness course. Depending on the kind and

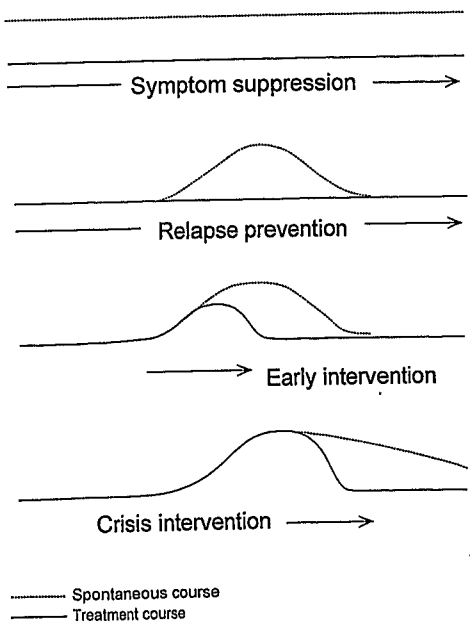


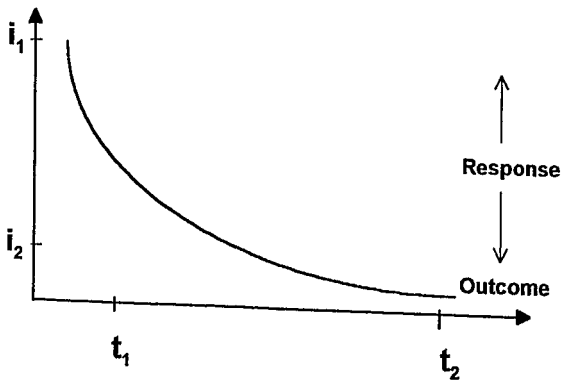

**Fig. 2.** Treatment interventions and illness course

time course (e. g. latency) of treatment effects, target symptoms, treatment duration, and time frame of measurement have to be adapted. Different therapeutic interventions depend on the illness stage. Acute treatment (early intervention, crisis intervention) and long-term treatment (symptom suppression, relapse prevention) can then be distinguished (Fig. 2).

### *Acute treatment*

Symptom change measured as a function of time [$f(t_1-t_2)$] may be the result of spontaneous remission, placebo response or treatment response. Therefore, in evaluating drug treatment effects response "on drug" has to be distinguished from response "to drug" (May and Goldberg 1978). This, however, is impossible in the individual case, if not an experimental A-B-A treatment design is applied.

In acute drug treatment, signs and symptoms of a given disorder are the target areas for measuring response. Usually, they are combined in a syndrome score or total score of a rating scale – reflecting global illness intensity (i) – which is applied repeatedly, at least once at the beginning and once at the end of a trial (Fig. 3).




**Change (f ($t_1$ - $t_2$)) by:**
- ♦Spontaneous remission
- ♦Placebo response
- ♦Drug response (on vs to drug)

**Measures of:**

| | | |
|---|---|---|
| ♦Course: | $\Delta i/\Delta t$, t 0 (i = signs/symptoms) | |
| ♦Outcome: | Residual score (RS) $i_2$ | |
| ♦Response: | Difference score (DS) | $(i_1 - i_2)$ |
| | Percent change (%C) | $(i_1 - i_2) \times 100 / i_1$ |

**Operationalization of:**

| | |
|---|---|
| ♦Response: | >= X %C |
| ♦Non-Response: | < X %C |

Fig. 3. Schematic illness course under acute neuroleptic treatment

Whereas outcome is indicated by the residual scale score $i_2$ at $t_2$, response is measured by means of a difference score ($i_1$–$i_2$) or by percent change [($i_1$–$i_2$)x100/$i_1$] to correct for interindividual differences in the initial scale score $i_1$. Response may then be operationally defined by a certain amount of percent change which has to be met, otherwise non-response would be inferred. However, it has to be kept in mind, that these definitions are arbitrarily applied to a continuum of response.

Comparable to global response statements such as "better" or "worse", there are at least two potential disadvantages of composite scale scores. First, the mixture of signs and symptoms blurs any differential effects of a drug, informing just about change in illness severity. Second, signs and symptoms are sampled from different data sources: The former are directly observable by the rater and can be measured or coded, the latter rely on the patient's introspection and verbal abilities (Alpert 1985). Not only from the viewpoint of reliability, but also validity, signs (i. e. objectively monitored illness behaviors) might be sometimes more preferable than patients' selfreports. With respect to a more "functionally" oriented psychopathology (Van Praag et al. 1987) aiming at underlying neurobiological dysfunctions and their responsivity to drug, target areas of drug response should be conceptually refined and subjected to objective measurement under more experimental assessment conditions (Gaebel and Renfordt 1989).

Response to psychoactive drugs, such as typical neuroleptics, develops with a time delay depending on certain neurobiological changes (Freed 1988, Pickar 1988). However, if one looks at the exponential time-curves of change, the group of responders (*on* or *to* drug) appears to improve more rapidly than that of non-responders. It is not known, whether the longer time course of change in "non"-responders reflects the slow but natural self-limitation of an illness episode (accelerated by drug only in the case of responders), or whether it reflects a kind of partial (e. g. placebo) responding. Whatsoever, this observation could help to reconceptualize response/non-response in terms of differences in the underlying time-dependent biological processes relevant for spontaneous illness course and treatment reactivity as well.

### *Long-term treatment*

Under long-term treatment conditions prevention of relapse is the most important response criterion. The concept of relapse means reappearance of an acute illness episode of a predefined magnitude after remission, irrespective whether it requires rehospitalization or not. To index an illness episode, related concepts such as full or partial remission, prodromal symptoms and recovery have also to be defined. Moreover, clinical deterioration has to be distinguished from relapse. In depression research the term relapse has been applied to early deterioration after an acute episode, whereas symptom re-exacerbation after a

defined time period of remission has been termed recurrence (Frank et al. 1991).

Neuroleptic long-term treatment – usually of the kind of low-dose maintenance treatment, since intermittent early intervention treatment has not turned out equally effective (Pietzcker et al. 1993) – serves either for relapse prevention or symptom suppression. Accordingly, prediction of response (relapse prevention) under long-term treatment aims at the virtual drug mechanism of suppressing/preventing/delaying a relapse. Obviously relapse is not prevented by symptom suppression but instead by a delay of symptom reappearance (Hogarty et al. 1973). However, the neurobiological mechanisms of neuroleptic maintenance treatment are far from clear.

## Predictors

Besides treatment the spontaneous illness course is shaped and modified by various factors, which are referred to as potential outcome/response "predictors" sampled from a wide area of patient and environmental characteristics. Although mainly described in psycho-social terms, these predictors are not necessarily non-biological in nature. Since the kind and mechanism of their illness/treatment relationship is far from clear, the more preferable neutral term for them would be "non-drug" factors. However, there are other types of classification of predictors, e. g. state/trait, static/dynamic or subjective/objective. With respect to the illness course and its treatment pre-treatment and treatment-dependent predictors of response may be distinguished (Fig. 4).

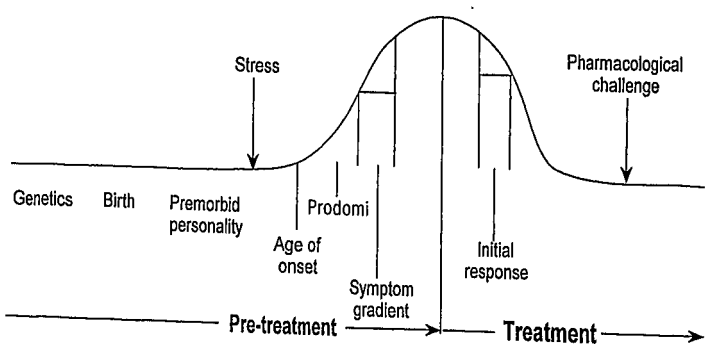



**Fig. 4.** Illness course and potential predictors of treatment response

If one conceptualizes the patient as a multilevel system in bio-psycho-social terms (Engel 1980), the following intervening levels may contribute to the complexities of drug treatment outcome (Fig. 5).

According to this model – besides environmental characteristics such

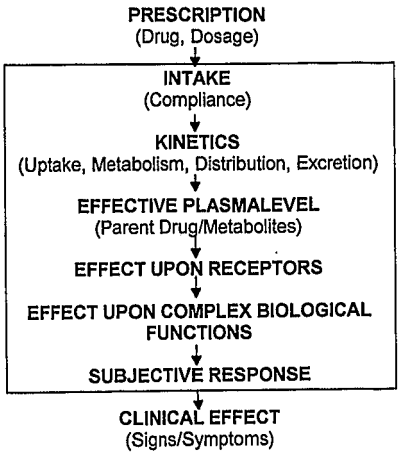



**Fig. 5.** Intervening system levels contributing to the complexities of outcome in drug treatment (from Helmchen and Gaebel 1987)

as treatment milieu, planned psychosocial interventions, and patient family environment (Gaebel 1993) – variables from all levels may be evaluated as potential outcome predictors (Table 1).

**Table 1.** Potential predictor variables (modified from Awad 1989)

| | |
|---|---|
| Patient | Demographics<br>(sex, SES, marital status)<br>Psychiatric history<br>(age of onset, family history, premorbid adjustment, prev. response)<br>Clinical characteristics<br>(Positive/negative symptoms, other symptoms)<br>Diagnostic criteria<br>Attitudes<br>(compliance) |
| Neuroleptic drug | Drug type |
| Effective plasma level | Drug blood levels<br>(test dose, steady state) |
| Effect at receptor | Indices of DA receptorblockade<br>(HVA, PRL, EPS)<br>Challenge tests<br>(GH, amphetamine) |
| Complex biolog. functions | Brain morphology<br>(CT, NMR)<br>Soft signs<br>Perinatal complications<br>Neurocognitive functions<br>Psychophysiology<br>(EDR, EEG) |
| Subjective interpretation | Early subjective response |
| Behavioral reactivity | Early symptom change |

Various chapters of this book deal with different kinds of predictors. Variables that measure atypical clinical features, chronicity, or past social performance have been identified as general prognostic indicators. Unfortunately, some of these predictors such as premorbid adjustment are often not easily distinguished from outcome itself, rendering their "predictive" value at least minimal. Moreover, most predictors have not been validated by replication studies (May and Goldberg 1978). Even with multivariate combinations of single predictors, usually no more than 30-40 % of the outcome variance has been explained. The beneficial effect of neuroleptic treatment seems to override the power of most predictors, i. e. most patients improve at least partially despite unfavorable characteristics. In the individual case, however, prediction of treatment success is particularly difficult. This may be explained by the extensive interindividual variability of treatment-related intervening processes (Fig. 5). Accordingly, in addition to static background variables without direct bearing on the treatment process itself treatment-related dynamic variables have been introduced into predictive models (May et al. 1976). They refer to cybernetic principles of the underlying illness process and its treatment-responsiveness (e. g. Selbach 1961) or the "elasticity" of biological systems as measured by PET (Dewey et al. 1993).

The so-called test dose model combines several predictors from different assessment levels, e. g. early psychopathological response, subjective response, pharmacokinetic, psychophysiological, biochemical, and other functional predictors after test dose application (Gaebel et al. 1988). Findings on the relationship between (early) pharmacokinetic data and treatment outcome are inconsistent (Gaebel et al. 1992) and may ultimately be replaced by more direct measures of drug effects at the receptor. Early subjective response has turned out as a response predictor in some studies (e. g. Van Putten and May 1978, Awad and Hogan 1985), but not in others (Gaebel et al. 1988). One of the more easily accessible and also replicated parameters is the early clinical response (May et al. 1980, Nedopil and Rüther 1981, Möller et al. 1983, Woggon and Baumann 1983, Awad and Hogan 1985, Bartko et al. 1987, Gaebel et al. 1988). From these findings it must be concluded, that – contrary to the imputed "latency" of neuroleptic response – specific clinical improvement takes place already in the first few days of treatment.

## Predictor-outcome relationships

The scientific meaning of statistical associations between predictors and outcome is far from clear. Generally, most of the "predictors" are "indicators" of unknown processes, relating in unknown ways to various outcome dimensions. Many of these relationships depend on the particular definition and operationalization of outcome or response – they change by altering such definitions. The scientific status of a predictor is almost never that of an outcome/response "determinant" – it is at best a statisti-

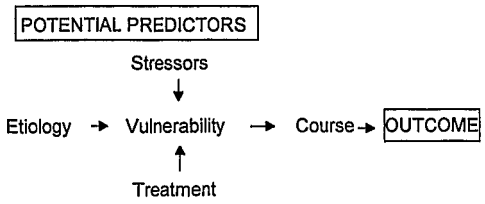



**Fig. 6.** Modified vulnerability-stress-model for use in prediction research

cally associated "risk factor" for treatment success/failure and/or side-effects, or an unspecific "indicator" of treatment response itself.

A heuristic integrative concept for prediction research is the vulnerability-stress model (Nuechterlein 1987, Clements and Turpin 1992). According to this model, pathogenetic as well as pathoplastic (Birnbaum 1923) determinants of illness course and treatment response (predictors) can be conceptualized on a biological, psychological and environmental level (Fig. 6).

To assess the relationship between treatment and response the concept of vulnerability – referring to a predisposition for psychic destabilization – has to be translated into the concept of instability. Potential clinical instability and hence relapse-proneness – thought to be mediated by a dysfunctional status of the dopaminergic system – can be assessed by the reactivity of the psychobiological system to pharmacological probes, e. g. methylphenidate (Lieberman et al. 1987). In a functional context the steepness of the symptom gradient of spontaneous destabilization as well as of drug-induced (early) restabilization are also predictors of treatment response. This kind of objective predictors are even more important since subjective antecedents of destabilization such as prodromal symptoms have not turned out as valid relapse predictors (Gaebel et al. 1993).

It is a task for future research to redefine in neurobiological terms the various predictor variables which have been proven effective. The final common pathway of drug and non-drug related influences on illness course may ultimately be reflected by postsynaptic regulatory processes of signal transduction and gene expression, which constitute plasticity in a given neural network (Hyman and Nestler 1993). It is possibly these processes which build the more enduring "structural" basis for different types of treatment outcome – and its prediction.

## Future research recommendations

To further scientific development in the field of prediction research, potential predictors of treatment response should be routinely included in clinical trials (Carpenter et al. 1981). According to the bio-psycho-social

model of etiopathogenesis and treatment (Engel 1980, Goodman 1991), which is now generally accepted in psychiatry, the various components of the vulnerability-stress-outcome model should be conceptualized and defined in biological and non-biological terms as well. Generally, a hypothesis-driven functional approach should be given more attention in prediction research: testing the function of a treatment relevant psychobiological system could reveal more about the capacity of responding to treatment than any epidemiological variable, which is at best an indicator of as yet not understood course modifying processes.

Finally, to make study results better comparable, the calculation of sensitivity (true positive rate) and specificity (true negative rate) of a predictive measure with respect to different cut-off points of predictor and outcome variables should be encouraged. The so-called ROC method (Receiver Operating Characteristics) allows to quantitatively assess and compare the significance of different outcome predictors (Hsiao et al. 1989). Generally, appropriate statistical methods should be applied to prediction research (see chapter by Köpcke).

## Conclusions

The clinical picture and (treatment) outcome of schizophrenia are heterogeneous and variable. Neuroleptic treatment response is a complex, in its pathophysiology still poorly understood and inconsistently operationalized phenomenon. Reliability and validity of many predictors are rather low, particularly in the individual case. Most patients (60–70 %) respond to typical neuroleptics; therefore, developing predictors of non-response or severe side-effects is of special importance. At present, predictions can best be made from psychobiological changes after test dose, pharmacological challenge or from previous treatment response. Future prediction research should prospectively assess potential predictors derived from the vulnerability-stress-model – defined in biological, psychological and social terms, using adequate methods for statistical analysis.

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